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Early Genetic Testing for HCM May Often Lead to Misdiagnoses

Larry Hand | August 18, 2016

BOSTON, MA — Early targeted genetic testing for hypertrophic cardiomyopathy (HCM) led to misclassification of benign genetic variants as pathogenic and to frequent misdiagnoses in a US study[1].

"While it is known that genetic diagnosis can be imperfect, our findings suggest that the burden of genetic misdiagnosis may fall disproportionately on African Americans," Dr Arjun K Manrai (Harvard Medical School, Boston, MA), told **heart*wire*** from Medscape by email. "Clinicians should have access to updated information and changes in variant interpretation, especially as new studies systematically reexamine known and novel variants using sequence data from diverse populations."

Manrai and colleagues conducted an analysis of sequence data on about 8500 individuals in three US national databases: the National Heart, Lung, and Blood Institute's Exome Sequencing Project, the 1000 Genomes Project, and the Human Genome Diversity Project. In addition, they reviewed clinical records of patients with HCM and family members tested at the Laboratory for Molecular Medicine, Partners HealthCare, in Boston, between 2004 and 2014.

In the database analysis, they found that five benign genetic variants accounted for 75% of genetic variation across all populations, but that these five mutations occurred disproportionately in African Americans. Between 2.9% and 27% of African Americans carried one or more variants, compared with 0.02% to 2.9% of white Americans.

At the laboratory, seven patients—five African Americans and two of unspecified ancestry—had been told they harbored disease-causing mutations but were later reclassified as having benign variants.

The results were published in the August 18, 2016 issue of the *New England Journal of Medicine*.

"Our findings point to the value of detailed clinical evaluations that go hand-in-hand with genetic testing," Manrai said. "There is a gap between genetics research and practice."

He continued, "Genetic testing can have profound consequences on patients and families. For HCM, genetic testing determines which family members are at risk and which are not and resolves clinically ambiguous cases. Correct classification is paramount."

Manrai said physicians should be telling their patients that "it is crucial to stay in contact with your genetic counselor or physician even after a positive genetic diagnosis. Our knowledge about the disease risks conveyed by genetic variants is evolving."

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*Follow Larry Hand on Twitter: @LarryHand16. For more from **theheart.org**, follow us on Twitter and Facebook.*

References

1. Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med* 2016; 375:655-665. Abstract

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